Jpn J Human Genet **38**, 345–349, 1993

Letter to the Editor

Origin of the Adjacent 1 Disjunction

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To investigate individuals heterozygous for reciprocal translocations is one object of prenatal diagnosis because of the high risks inherent in chromosomally unbalanced offspring (Boué and Gallano, 1984; Daniel *et al.*, 1988). In genetic counseling, it is important to estimate the percentage risk of having such offspring (Fuhrmann and Vogel, 1982; Harper, 1988). The risks may depend on events including various ratios of cells with an unbalanced chromosome constitution resulting from segregation from quadrivalents, the lack of unbalanced gamete participation in fertilization, and selection of unbalanced embryos during the period from early embryogenesis to later development.

Segregation ratios from quadrivalents in tanslocation heterozygotes have often been discussed on the basis of cytogenetic data from offspring and fetuses of translocation carriers (Petrosky and Borgankar, 1984; Stene and Stengel-Rutkowski, 1988). The chromosome segregation in male translocation heterozygotes has also been studied by sperm chromosome analysis using the hamster oocyte-human sperm fusion technique (Martin, 1988; Spriggs *et al.*, 1992). Several authors have described that, when the genotype of offspring and sperm are normal or balanced, the gamete derived from alternate disjunction in the translocation heterozygote. When the genotype is unbalanced, on the other hand, they assume that the gamete originated from the adjacent 1, 2, or 3:1 disjunction. In this really the case?

In studies of offspring or sperm in translocation heterozygotes, however, no one has obtained data of meiotic crossing-over, except in a few individuals with specific karyotypes from adjacent 2 and 3:1 disjunctions accompanying crossing-over, which are usually rare (Lindenbaum, 1990; Spriggs *et al.*, 1992). A meiotic crossing-over can not usually be detected as a specific change of the karyotype in gametes and zygotes. In particular, when the alternate disjunction occurs accompanying meiotic crossing-over at the "interstitial" (in this letter, a segment between the centromere and a break point in a derivative chromosome) segment in translocation heterozygotes, the derived karyotypes seen in gametes and zygotes might be indistinguishable from those derived from the adjacent 1 disjunction accompany-

Received April 22, 1993; Accepted May 7, 1993.

ing no crossing-over (Fig. 1). The reverse is also true.

By direct chromosome analysis of the second meiotic (MII) cells, we investigated chromosome segregation in heterozygotes for various reciprocal translocations in the Chinese hamster (Sonta *et al.*, 1984, 1991b). Among individuals heterozygous for unequal reciprocal exchanges, marker chromosomes with chromatids of unequal length are seen in MII cells as a result of crossing-over on the "interstitial" segments of translocation chromosomes (Fig. 1). The results of crossing-over estimated by MII analysis in translocation heterozygotes using 8 strains with different reciprocal translocations are summarized in Table 1. Numbers of crossing-over on each "interstitial" segment per cell ranged from 0.07 to 0.99, and the mean was 0.51. Crossing-over on the "interstitial" segments is not uncommon.

In reciprocal translocations, the "interstitial" segment includes the region from the centromere to the exchanged point in each derivative chromosome. Thus, in a reciprocal translocation exchanged at the distal end of one chromosome arm,

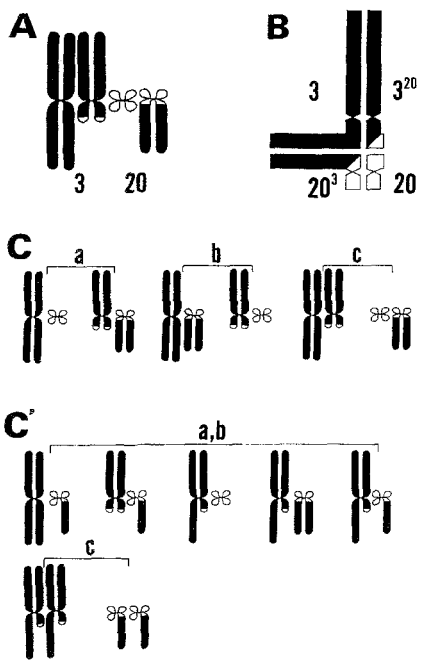

Fig. 1. Schematic representation of chromosome segregation in an example heterozygous for a t(3;20) reciprocal translocation. A: A partial karyotype from the translocation heterozygote. B: A scheme of the quadrivalent derived from the translocation. C: Partial karyotypes seen in MII cells derived from various disjunctions, alternate (a), adjacent 1 (b), and adjacent 2 disjunctions (c). The 3:1 disjunction is excluded. C′: Karyotypes derived from the same disjunctions accompanying crossing-over on the interstitial segments. The chromosome constitutions derived from alternate and adjacent 1 disjunctions are indistinguishable.

the "interstitial" segment must be almost the same as the whole arm. In individuals heterozygous for such reciprocal translocations, the frequency of meiotic crossing-over on some chromosome arms estimated by MII marker chromosomes was almost equal to that of chiasmata on the same arms in karyotypically normal males (Table 1).

The mean number of chiasmata on each chromosome in male Chinese hamsters ranged from 0.88 to 2.68 (data not shown). In human males, on the other hand, the mean number of chiasmata on each chromosome ranged from 1.05 to 3.90 (Paris Conference, 1971), which reveals that an average of more than one crossing-

Table 1. Frequency of crossing-over on the interstitial segments (IS) in males heterozygous for various reciprocal translocations and the mean number of chiasmata in the same chromosome arm in karyotypically normal male Chinese hamsters.

Heterozygote[a]	Translocation chromosome	Frequency of cross-over on the IS/quadrivalent[b]	Mean number of chiasmata on the normal bivalents[c]
T12/+	1^{2}	0.81	—
	2^{1}	0.23	—
T13/+	2^{4}	0.62	—
	$\underline{4^{2}}$	0.75	0.76
T20/+	4^{8}	0.39	—
	$\underline{8^{4}}$	0.42	0.44
T23/+	1^{6}	0.65	—
	$\underline{6^{1}}$	0.99	1.02
T26/+	3^{9}	0.23	—
	9^{3}	0.07	—
T31/+	1^{5}	0.56	—
	$\underline{5^{1}}$	0.97	1.02
T41/+	2^{3}	0.18	—
	3^{2}	0.22	—
T52/+	2^{7}	0.75	—
	$\underline{7^{2}}$	0.99	1.02

[a] Refer to Sonta *et al.* (1991a). The translocation chromosomes marking with underlines exchanged at the distal end of normal chromosome arms. [b] In a t(1;2) translocation, for a instance, the frequency of crossing-over on the interstitial segment of 1^{2} was calculated as

$$\frac{\text{Number of cells with chromosome } 1'}{\text{No. of cells with chromosomes 1, } 1^{2}\text{, and } 1'.}$$

Chromosome 1′ is a marker having unequal-length chromatids resulted from crossing-over on the IS of 1^{2}. [c] Showing half of the mean number of chiasmata in medium and small bivalents originating from biarmed B- and D-group chromosomes (nos. 3 and 4, and nos. 8–10), and the mean number of chiasmata of medium bivalents originating from acrocentric C-group chromosomes (nos. 5–7).

over event may occur on each chromosome arm. That is, the frequency of meiotic crossing-over per chromosome in human males is not lower than that in male Chinese hamsters. These facts therefore suggest, that meiotic crossing-over may also occur commonly on the "interstitial" segments in humans heterozygous for reciprocal translocations as well as in Chinese hamsters, and so the segregants from translocation heterozygotes may very often have karyotypes resulting from disjunctions accompanying crossing-over on the "interstitial" segments. Recently, Goldman and Hultén (1993) have used testicular material to investigate chiasma frequency and meiotic segregation in a human male heterozygous for a t(1;11) reciprocal translocation, and found actually that about 70% of MII cells with products of alternate and adjacent 1 disjunctions accompanied interstitial crossing-over.

Table 2 shows the frequencies of gametes with various karyotypes derived from alternate and adjacent 1 disjunctions in an example with a t(1;2) reciprocal translocation. The frequencies are estimated on the assumption that the crossing-over on the interstitial segments occurs with various combinations of the frequencies (0, 50, or 100%). This example reveals that a large proportion of gametes and zygotes with karyotypes that look as though they originated from an adjacent 1 disjunction may in fact have originated from an alternate disjunction accompanying crossing-over. The karyotype analysis of gametes and zygotes cannot determine this. In other words, whether the genotype really originated from an alternate or adjacent 1 disjunction cannot be distinguished, since meiotic crossing-over might occur frequently on each "interstitial" segment. When studying chromosome segregation by chromosomal analysis of gametes and zygotes from individuals heterozygous for reciprocal translocations, therefore, the origins as alternate and adjacent 1 disjunctions should be bundled together, except for specific individuals in which

Table 2. Frequency of gametes with various karyotypes derived from alternate and adjacent 1 disjunctions in an example with a t(1,2) translocation.[a]

Genotype of gamete	Cross-over on IS of 1^2 and 2^1[b]			
	(0,0)	(50,0)	(50,50)	(100,0)
(1,2)	30 (0)[c]	25 (2.5)[c]	22.5 (3.75)[c]	20 (5)[c]
(1^2,2^1)	30 (0)[c]	25 (2.5)[c]	22.5 (3.75)[c]	20 (5)[c]
(1,2^1)	10 (10)[c]	15 (7.5)[c]	17.5 (6.25)[c]	20 (5)[c]
(1^2,2)	10 (10)[c]	15 (7.5)[c]	17.5 (6.25)[c]	20 (5)[c]

[a] Supposing that the true frequencies of alternate and adjacent 1 disjunctions are 60 and 20%, respectively. The frequency of gametes with each karyotype was estimated on the assumption that each chromatid separates equationally at anaphase II. [b] The supposed frequency of crossing-over on the interstitial segment (IS) of chromosomes 1^2 (a) and 2^1 (b) is shown as (a, b), respectively. [c] The frequencies of gametes that truly originated from an adjacent 1 disjunction in each, are shown in parentheses.

the existence of crossing-over on the interstitial segments has been confirmed by some genetic markers.

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